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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/649,299	CORBETT ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Art Unit: 1624

DETAILED ACTION

Election/Restrictions

Claims 2-4 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 31 July 2007.

Applicants' reply to the Requirement for Restriction which was mailed 1 July 2005, has been noted. It is acknowledged that claim 8 is indeed drawn to a method, not a compound according to Group I of the Requirement.

Applicants' reply to the requirement for an election of single disclosed species is acknowledged as well. Applicants have indicated election of the compound 3,6-diethyl-N-[(1R,2S)-2-(2-fluoroethoxy)-2,3-dihydro-1*H*-inden-1-yl]5-[(4-methylpyridin-2-yl)oxy]pyrazin-2-amine. The compound was searched, and no prior art was found, whereupon the search was broadened and expanded, eventually to include the scope of all of claims 1, 5-7 and 9-15. So, claims 10-13 have not been withdrawn from consideration. The claims of elected Group I, however, are not in allowable form, due to the rejections set forth hereinbelow, so conditions necessary for rejoinder of the claims non-elected without traverse have not been satisfied. A reply to this Office action which satisfactorily addresses the issues raised in the rejections will prompt rejoinder of claims 2-4 and 8 (see section headed "comments" below).

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-7 and 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds according to Formula I and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for prodrugs of Formula I compounds, in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

When the Office makes a determination of whether or not a claimed invention is enabled by the accompanying disclosure, an analysis of the factors promulgated by the court in the *In re Wands* decision are customarily relied upon. These so-called "Wands factors" are as follows, and each in turn will be addressed for prodrugs and solvates:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Prodrugs are not Enabled:

(A) Though it might appear that the 'prodrugs' embodiment of instant claims 1, 5-7 and 9-15, would be limited only to compounds which are actually embraced by the Formula I molecular structure diagram, it is not.

A prodrug, as defined by Bundgaard in:

> Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of compounds according to the instant claims is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only ester derivatives, which are commonly cited as examples, and are suggested as such at page 13, lines 6-10 of the specification. A prodrug may also be an acyclic precursor to a heterocyclic compound, a Mannich base (imine), a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug. A prodrug is *any* compound which is converted into the parent drug *in vivo*.

So, the scope of all prodrugs is quite broad. A prodrug does not necessarily depend on the identity of the pharmacologically active agent formed *from* the prodrug for patentability. A prodrug is not necessarily even structurally related to the compound of which it functions as a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of compounds described in claims 1, 5-7 and 9-15 are the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

> Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.

Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug is

desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art insofar as the prodrug embodiment of instant claims 1, 5-7 and 9-15 is concerned is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the other hand, when a compound is designed as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically derived when the compound in question is an (allegedly) novel compound, as are compounds according to claims 1, 5-7 and 9-15. It cannot be predicted which compounds will serve as prodrugs of the compounds named in claims 1, 5-7 and 9-15.

(F) No guidance *specific* to the preparation of prodrugs of compounds according to claims 1, 5-7 and 9-15 is provided in the specification.

No metabolic studies of the compounds *in vivo* have been reported in the specification and no structure-activity rules are outlined – certainly no teaching as to which modifications will afford an *inactive* compound is found in the specification. The specification does not specifically address any type of prodrug other than ester derivatives, amine derivatives, or sulfhydryl derivatives, which basically all are descriptive of ester or amide derivatives.

(G) No working examples of a prodrug are disclosed.

(H) In order for one of ordinary skill in the art to be able to make the full scope of all prodrugs of compounds of claims 1, 5-7 and 9-15, a complete structure activity analysis of all the millions of compounds embraced by Formula I according to claim 1 would have to be completed. The practitioner would first screen for which modifications would render an inactive compound, for each compound. In doing so, for each compound, there would potentially be hundreds of different derivitizations to study. Then, metabolic studies of all of these inactive compounds would have to be completed, and compounds that are converted back into the compounds named in claims 1, 5-7 and 9-15, *in vivo*, identified. This research would potentially be inconclusive and could take years. Another part of the work necessary for realizing the full scope of prodrugs of compounds according to claims 1, 5-7 and 9-15 would be that pertaining to totally new compounds not bearing any structural similarity to those compounds, such as the *pro*cyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with many different types of polymeric forms (both ionically bound and covalently bound) of the compounds of claims 1, 5-7 and 9-15 would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics (drugs, in other words) are handled by different enzymatic pathways, this effort would have to be duplicated in each

species for which a prodrug of a compound according to claims 1, 5-7 and 9-15 were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

> Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations." Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the paltry amount of direction in the disclosure, the amount of experimentation required to realize the full scope of claims 1, 5-7 and 9-15 is clearly undue. Applicants have not described the manner and process of making prodrugs of compounds named in claims 1, 5-7 and 9-15, in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

Claims 1, 5-7 and 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "prodrug thereof," in reference to Formula I compounds, recited in instant claim 1, renders the claims indefinite in scope.

Although some fairly obvious "prodrug" candidates could be identified by one of ordinary skill (e.g., acetate, formate and benzoate derivatives, as taught at page 13, lines 8-10 of the specification), the *full scope* of *all* molecular structures which would and could yield a compound according to claims 1, 5-7 and 9-15 upon metabolism in some

(unidentified) animal is not readily apparent from a reading of the claims in light of the specification.

Simply because one of ordinary skill in the art understands what *function* a prodrug serves or what the word "prodrug" means is not enough to apprise him of what *molecular structures* lie within the scope of claims 1, 5-7 and 9-15 and what structures lie without. The specification does not provide any teachings specifically applicable to the compounds disclosed therein which will render the claimed prodrugs. No metabolism studies of the compounds of the present invention are disclosed in the instant specification either.

A rejection of the term "prodrugs" under the first paragraph of this statute precedes this indefiniteness rejection of the same term. Applicants' attention is directed to section "A" – the breadth of the claims – for an explanation of what is actually contemplated by "prodrug." It contemplates more than simply of the compounds such as those suggested in page 13 of the specification. This rejection is not being made in view of the breadth of the term "pharmaceutically acceptable forms" but rather because of the complexity that the term adds to the claim. One of ordinary skill in the art, to be apprised of what is actually covered by the claims, would have to be aware of <u>all</u> chemical compounds which would or could be metabolized into each and every named compound in claims 1, 5-7 and 9-15 in <u>any</u> animal species, which is practically impossible, because for each named compound in claim 1, 5-7 and 9-15, there would be an innumerable amount of possible molecular arrangements which could yield the said compounds upon metabolism in an animal. These molecular arrangements would be different for different kinds of animals (this point is raised in the preceding rejection of "prodrugs" under the first paragraph of this

statute – see point (H)), further confounding any attempt at determining exactly what compounds claims 1, 5-7 and 9-15 embrace.

Claims 1, 5-7 and 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5-7 and 9-15 are further indefinite, in addition to being indefinite for recitation of "prodrug thereof" because claim 1, from which all of claims 5-7 and 9-15 depend, specifies that "alkyl" means both straight- and branched chain hydrocarbon chains having from 1 to 10 carbon atoms, while "cycloalkyl" is specified as being "a monocyclic or bicyclic alkyl moiety having from 3-10 carbon atoms, optionally containing 1 to 2 double bonds provided that the moiety is not aromatic..." The claim defines "alkyl" not having double bonds, while "cycloalkyl" may contain double bonds. A double bond-containing hydrocarbon group which is not aromatic would be referred to as a cycloalk*ene*, in chemical parlance.

The same problem exists for "aryl cycloalkyl" and "heterarylcycloalkyl," namely that the definitions recited for those terms provide for double bonds in the cycloalkyl ring.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947); *Ex Parte Clifford*, 63 USPQ 19. Terms may not be "used in ways that are contrary to the accepted meanings in the art" (MPEP 2173.01).

It has been assumed in the examination that applicants intend the term "cycloalkyl" to actually embrace "cycloalkyl" and furthermore to embrace "cycloalkenyl." The same

holds true for "heterocycloalkyl," and "aryl cycloalkyl" heteroaryl cycloalkyl" being embracive of "heterocycloalkenyl," "aryl cycloalkenyl" and "heteroaryl cycloalkenyl," respectively.

Claims 1, 5-7 and 9-15 are further indefinite, in addition to being indefinite for recitation of "prodrug thereof" because claim 1, from which all of claims 5-7 and 9-15 depend, recites the language "... and further provided that the double bonds are not cumulated;" in the definition of the term "cycloalkyl." Exactly what this signifies is not understood.

Claim 7 is further indefinite, in addition to being indefinite for recitation of "prodrug thereof," for the reason that there is no "standard" assay of CRF binding. Documents cited in the Information Disclosure Statement (for example, Vale et al, *Recent Progress in Hormone Research*, vol. 39, pages 245-270 (1983) and Nemeroff et al, Archives of General Psychiatry, vol. 45, pages 577-579 (1988)) filed with the instant application refer to many different methods of assaying CRF binding.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-7, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/76980 (Murakama et al).

The Murakama et al publication discloses compounds according to instant claims 1, 5-7 12 and 13, wherein V is –NH-; "Ar" is phenyl, substituted with methyl or nitro; R_1 is -

NH(substituted alkyl) - 2-(N,N-dimethylaminoethyl); R_2 is $-C(O)NR_4R_5$, $-CONH_2$; and "X" is $-CR_3R_5R_5$, methyl or ethyl, or n-propyl.

Claims 5-7 are included in this rejection because the specification teaches, generally, that compounds within the scope of Formula I have the properties recited in those claims.

Further Comments

Upon receipt of a reply to this Office action which satisfactorily rebuts and/or (preferably) amends the scope of the claims to obviate the rejections set forth herein, the claims of nonelected Group II as set forth in the Requirement for Restriction will be rejoined and the Requirement will be withdrawn.

The rejoinder and examination of the nonelected claims will present new patentability issues under the first paragraph of 35 U.S.C. 112, particularly with respect to claims 3, 4 and 8. CRF_1 receptor antagonists, at the time the invention was made, were not known to be effective for *preventing* any physiological disorder, as recited in instant claim 3, only *treatment* of a few, namely anxiety and depression.

In claim 3 also, there is a recitation that the method is drawn to treatment of physiological disorders resulting from insufficient CRF. Since the compounds of the present invention are CRF receptor antagonists, it is not understood how they could be employed as a therapeutic agent for the treatment of a condition which results from too little CRF; it is contrary to the mode of action of the compounds of the present invention to suggest that they could be a therapeutic agent for the treatment of a condition which results from too little CRF secretion.

The term "stress," as recited in claim 8, generally, and without some sort of context,

is not a distinct and clear medical term, rather the distinction between the presence and absence of stress, or between different kinds of stress is blurred, and treatment of all of the different types of stress within the broadest reasonable interpretation of the term does not appear to be enabled by the disclosure in light of the state of the art in CRF antagonist agents at the time the invention was made.

Two references which will provide an assessment of the state of the art and level of skill in the field of CRF receptor antagonists at the time the invention was made are:

> Dautzenberg and Hauger, "The CRF peptide family and their receptors: yet more partners discovered" Trends in Phamacological Sciences, vol. 23(2), pages 71-77 (February 2002).
>
> and,
>
> Kehne and De Lombaert, "Non-Peptidic CRF_1 Receptor Antagonists for the Treatment of Anxiety, Depression and Stress Disorders" Current Drug Targets - CNS & Neurological Disorders, vol. 1(5), pages 467-493 (2002).

The references are enclosed with this Office action.

Claim 4, which refers to a method of inhibiting CRF binding to the CRF_1 receptor, does not meet the requirements of the first paragraph of 35 U.S.C. 112, insofar as the "how to use" portion of the statute is concerned. Exactly how one of ordinary skill would use the method according to instant claim 4 is not set out in the instant specification. It is clear that treatment of more than anxiety and depression is intended to be embraced by the method according to instant claim 4, yet no other specific disorders (save "stress," – on page 4 – which is indefinite; and smoking cessation) are mentioned in the specification, specifically with respect to the compounds according to the present invention.

Allowable Subject Matter

Upon obviation of the rejections set forth herein, the application will be re-examined insofar as the rejoined claims are concerned. Applicants' amendment of the withdrawn

claims to reflect the understanding of the state of the art with respect to the therapeutic application of CRF receptor antagonists, at the time the invention was made, would be appreciated. Cancellation of claims 3 and 4, and amendment of claim 8 so as to delete the term "stress" would be appreciated.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 9:00am to 5:00pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Zachary C. Tucker/
Primary Examiner, Art Unit 1624